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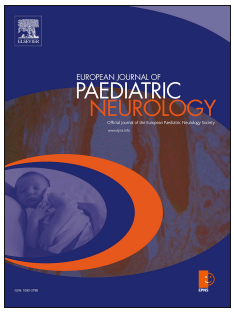

Progression to Musculoskeletal Deformity in Childhood Dystonia

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Article Title:

Progression to Musculoskeletal Deformity in Childhood Dystonia

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Abstract

Aim

Dystonia is a movement disorder characterized by involuntary muscle contractions, resulting in abnormalities of posture and movement. Children with dystonia are at risk of developing fixed musculoskeletal deformities (FMDs). FMDs cause pain, limit function and participation and interfere with care. We aimed to explore factors relating to the development of FMD in a large cohort of children with dystonia.

Method

The case notes of all children referred to our Complex Motor Disorder service between July 2005 and December 2011 were reviewed. Data from 279 children (median age 9 years 10 months, Standard Deviation 4 years 2 months) with motor disorders including a prominent dystonic element were analysed. Parametric accelerated failure time regression was used to identify the factors related to development of contractures.

Results

FMDs were present at referral in more than half (n=163, 58%) of cases. Three quarters (n=120, 74%) of children with FMD had deformities around the hip, and 42% had spinal deformity (n=68). Compared to pure primary dystonia, FMD onset was earlier with a diagnosis of secondary or heredodegenerative dystonia, and a mixed spastic-dystonic phenotype (all $p<0.001$). FMD onset was also earlier with increasing Gross Motor Function Classification System (GMFCS) level ($p<0.001$).

The effect of aetiological classification was lost when controlling for GMFCS level and motor phenotype.

Interpretation

Children with secondary or heredodegenerative dystonia are at greater risk of progression to FMD compared to primary dystonia, likely due to more severe dystonia within these groups. Children with additional spasticity are at particular risk, requiring close monitoring.

Dystonia is characterized by *"sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both"*[1]. Dystonia has most commonly been classified on an aetiological basis as "primary", "primary-plus", "secondary" or "heredodegenerative"[2]. In primary dystonia, dystonic movements are the only abnormality, in the absence of any exogenous cause and with normal neuroimaging. In Primary-plus dystonia other abnormal movements are present.[3] Secondary dystonia is a symptomatic disorder, arising due to a disease processes affecting the brain, often with additional neurological features. Heredodegenerative dystonias are those arising in the context of progressive neurodegeneration. Secondary dystonias are more common in childhood[4 5]. Whilst a move away from this terminology has recently been proposed[1], it remains a useful way to classify dystonias from diverse aetiologies into groupings with common features for comparative work.

Dystonia in childhood can interfere with all domains of the International Classification of Functioning, Disability and Health (ICF) framework[6 7], including impairment, activity and participation, with significant implications for future adult life.

In general, hypertonic movement disorders are associated with the development of fixed musculoskeletal deformity (FMD). FMDs cause pain, limit function, impair sleep and create difficulties with care. Without effective intervention, progression of FMD and worsening impairment of function will occur[8-10], though the rate of this progression varies for each individual. Cerebral palsy (CP) has been the focus of much of the work around FMD development, which has been related to increasing impairment of function[11 12]. Most studies have focused on patients with

predominantly spastic motor disorders (the most common impairment in CP), with only small numbers of children with dystonic CP included. Large studies of FMD in children with dystonia are absent. We aimed to explore which clinical factors were related to the development of FMDs in a group of children and young people (CAYP) referred to our supra-regional complex motor disorder service (CMDS).

Method

All CAYP assessed by our CMDS between June 2005 and December 2012 were considered for inclusion in this study. Our service offers a supra-regional referral service for CAYP with dystonic motor disorders, primarily with view to assessment for suitability for ITB/DBS. Demographic/clinical characteristics were extracted from patient case notes. Details of musculoskeletal examinations performed by three of the authors were reviewed (MK and JL, Paediatric Neurologists with > 10 years of experience, and KT, a Clinical Specialist Paediatric Physiotherapist with >10 years of experience working with children with complex neurodisability). Clinical features of CAYP in this cohort have previously been reported[5 7].

A pragmatic definition of FMD was used: Fixed deformity of a limb/joint impairing function due to contracture (i.e. permanent tightening of non-bony tissue) and not due to active contraction, restricting daily activity/participation and/or impairing the delivery of care whether through a direct restriction of movement or secondary to pain/discomfort. When present, FMDs were categorized on the basis of body region affected into i) hip, ii) spine or iii) peripheral. Deformity at multiple regions was recorded when present.

Details of CAYP diagnosis and aetiological classification were recorded. Motor-phenotype was classified as i) pure dystonia, ii) mixed dystonia-spasticity, iii) dystonia-choreoathetosis, iv) dystonia-myoclonus, v) dystonia with prominent tremor, or vi) dystonia-parkinsonism. CAYP deemed to have a purely spastic motor phenotype were excluded.

The Gross Motor Function Classification System (GMFCS) [13] was used to classify motor function. This scale has been validated for children with CP, and so should be considered "GMFCS equivalent" as not all children in this study had this diagnosis. For 132 patients dystonia severity had also been assessed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)[14]. Videotaped BFMDRS evaluations were scored by 2 clinicians, not blinded to other clinical/demographic details.

Statistical analysis was performed using the R language for Statistical Computing, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria), and the survival package, version 2.36-14 (Terry M. Therneau, Mayo Clinic, Rochester, USA) [15]. Age of FMD onset was considered to be interval censored between the age of onset of dystonia and age of referral to our service for CAYP with FMD at referral and right-censored at age of referral for CAYP without FMD at referral, based on the assumption of eventual progression to FMD over time [8 9]. Parametric accelerated failure time models using the log-normal distribution were fitted to identify which clinical factors led to an earlier or later onset of FMD. A parametric approach was chosen to give greater power to the analysis of the interval-censored observations. An accelerated failure time model was used both because the assumptions of a proportional hazards model were not met and because accelerated failure time models are more robust to model misspecification[16 17]. The log-normal model was chosen because it provided the best fit of 6 models considered. Modelling assumptions were checked using diagnostic plots and relevant statistics. Median event times, 95% confidence intervals and p-values were calculated. Aetiological classification, motor-phenotype, GMFCS level and age of dystonia onset were used

as covariates in the models – both in univariate and in multivariate models. Small subgroups of less than 20 patients (e.g. patients with Dystonia-Myoclonus, Dystonia-Choreoathetosis, Dystonia tremor, or Dystonia-Parkinsonism motor-phenotype) were merged together to produce sufficiently large groups for statistical modelling.

The study was registered as an audit with Guy's and St Thomas NHS Trust. Since the data were not personally identifiable, consent was neither required nor obtained. Data were permanently anonymised and handled according to Caldicott principles and the requirements of the Data Protection Act.

Results

Case notes were available for 294/320 (92%) CAYP referred to our service between July 2005 and December 2011, 15 of whom were excluded from further analysis due to a purely spastic motor phenotype. In the remaining 279 CAYP (summary and full details in Table 1), the majority (72%) had secondary dystonia, with primary dystonia (11%), primary-plus dystonia (7%) or heredodegenerative dystonia (10%). Pure dystonia was the most prevalent motor phenotype (58%), with mixed dystonia-spasticity the second most prevalent (28%). Age at referral was similar for all aetiological classifications. About two thirds (65%) of CAYP with primary or primary-

plus dystonias had GMFCS levels I-II, while about three quarters (72%) of patients with secondary or heredodegenerative dystonias had GMFCS level V.

Aetiological classification	Age at Referral Median (25%-75%)	Age of Onset Median (25%-75%)	Motor Phenotype	n	%	Functional Level (GMFCS)	n	%
All patients (n=279)	9.8 (6.6 to 13.0)	0.3 (0.1 to 1.4)	Dystonia	161	58%	I	26	9%
			Mixed Dystonia Spasticity	79	28%	II	26	9%
			Dystonia-Myoclonus	18	6%	III	14	5%
			Dystonia Choreoathetosis	16	6%	IV	40	14%
			Dystonia Tremor	3	1%	V	173	62%
			Dystonia Parkinsonism	2	1%			
Primary (n=30, 10.8%)	11.9 (8.2 to 14.9)	1.5 (0.2 to 6.9)	Dystonia	30	100%	I	8	27%
			Mixed Dystonia Spasticity	0	0%	II	11	37%
			Dystonia-Myoclonus	0	0%	III	4	13%
			Dystonia Choreoathetosis	0	0%	IV	2	7%
			Dystonia Tremor	0	0%	V	5	17%
			Dystonia Parkinsonism	0	0%			
Primary-Plus (n=19, 6.8%)	9.8 (6.5 to 12.6)	3 (1.0 to 6.0)	Dystonia	0	0%	I	10	53%
			Mixed Dystonia Spasticity	2	11%	II	3	16%
			Dystonia-Myoclonus	14	74%	III	1	5%
			Dystonia Choreoathetosis	1	5%	IV	3	16%
			Dystonia Tremor	0	0%	V	2	11%
			Dystonia Parkinsonism	2	11%			
Secondary (n=201, 72.0%)	9.5 (6.3 to 12.5)	0.2 (0.1 to 0.5)	Dystonia	111	55%	I	7	3%
			Mixed Dystonia Spasticity	73	36%	II	10	5%
			Dystonia-Myoclonus	3	1%	III	9	4%
			Dystonia Choreoathetosis	13	6%	IV	31	15%
			Dystonia Tremor	1	0%	V	144	72%
			Dystonia Parkinsonism	0	0%			
Heredodegenerative (n=29, 10.4%)	9.9 (6.8 to 13.0)	2.2 (0.8 to 4.0)	Dystonia	20	69%	I	1	3%
			Mixed Dystonia Spasticity	4	14%	II	2	7%
			Dystonia-Myoclonus	1	3%	III	0	0%
			Dystonia Choreoathetosis	2	7%	IV	4	14%
			Dystonia Tremor	2	7%	V	22	76%
			Dystonia Parkinsonism	0	0%			

Table 1. Demographic and clinical classification of 279 children with dystonia by aetiological classification. Percentages in the first column are out of all patients while percentages on the right are out of the subgroup shown in the first column. Because numbers are rounded the percentages may not sum up to 100%.

FMDs were present at referral in 163 (58%) cases (full details in Table 2). Amongst CAYP with FMD, deformity around the hip was most common (74%), followed by spinal deformity (42%). FMD was commonest in children with secondary or heredodegenerative dystonias compared to other diagnoses, mixed dystonia-spasticity compared to other motor phenotypes, and GMFCS level V compared to lower levels (Pearson's chi-squared tests for independence with small groups merged as in Fig. 1 all $p<0.001$).

BFMDRS motor scores were available for 132 (47%) CAYP (24 primary dystonia, 9 primary-plus dystonia, 83 secondary dystonia and 16 heredodegenerative dystonia). Higher BFMDRS scores were seen in the secondary and heredodegenerative groups (median 100 and 86 respectively) compared to primary and primary-plus groups (median 59 and 30 respectively, Kruskal-Wallis rank sum test $p<0.001$). The proportion of CAYP with FMD was lower in those for whom BFMDRS scores were available (FMD in 67/132, 51%), compared to those for whom BFMDRS scores were not available (FMD in 96/147, 65%, Pearson's chi-squared test for independence $P=0.014$).

Parametric accelerated failure time models were fitted by including one of aetiological classification, motor phenotype or GMFCS level as explanatory variable (Figure 1). Because they exhibited a similar time to FMD onset and individual groups were too small to model, the following groups were merged: the primary and primary-plus groups for aetiological classification, and the 1-2 and 3-4 groups for GMFCS, respectively. Also, because they were too small to model, the dystonia-myoclonus,

dystonia-choreoathetosis, dystonia tremor, and dystonia-parkinsonism motor phenotypes were merged into one group.

		Number of patients	Overall Deformity	Hips	Spine	Shoulder	Peripheral Contractures
All patients		279	58%	43%	24%	3%	35%
Aetiological Classification	Primary	30	23%	13%	3%	0%	20%
	Primary-Plus	19	5%	5%	0%	0%	0%
	Secondary	201	67%	50%	28%	3%	38%
	Heredodegenerative	29	69%	52%	38%	3%	48%
Motor Phenotype	Pure Dystonia	161	54%	35%	21%	2%	34%
	Mixed Dystonia-Spasticity	79	86%	75%	38%	4%	49%
	Dystonia-Choreoathetosis	16	38%	25%	25%	0%	12%
	Dystonia-Myoclonus	18	0%	0%	0%	0%	0%
	Dystonia Tremor	3	33%	0%	0%	0%	33%
	Dystonia Parkinsonism	2	50%	50%	0%	0%	0%
GMFCS	Level I-II	52	12%	6%	2%	0%	8%
	Level III-IV	54	41%	22%	7%	0%	30%
	Level V	173	78%	61%	36%	4%	45%

Table 2. Incidence of fixed musculoskeletal deformities in different body regions by aetiological classification, motor phenotype, and GMFCS level. The first column shows the absolute number of patients in each subgroup while the other columns show the percentage of these patients who have FMD either overall or in that specific body region. The shading of the cells is proportional to percent of all patients in the first column and percent of patients in that subgroup in all other columns.

Estimated onset of FMD occurred much earlier in both secondary (estimated median age 6 years, p<0.001) and heredodegenerative (estimated median age 7 years, p<0.001) groups than in the merged primary and primary-plus dystonia group (estimated median age >21 years). Median age at FMD onset decreased significantly with increasing GMFCS level (p<0.001): the estimated median age for levels 1-2 was >21 years, 10 years for levels 3-4, and only 5 years for level 5. Compared to CAYP with pure dystonia, with an estimated median age of 9 years at FMD onset, FMD onset occurs significantly earlier, at 4, for patients with mixed dystonia-spasticity (p<0.001). The other motor phenotypes generally show later onset of FMD, but are too heterogeneous to make a definitive statement. Full details including confidence intervals are provided in Table 3.

The GMFCS level gave the most discrimination in age of FMD onset, motor phenotype is the second most useful predictor. After allowing for the GMFCS level in the model, the inclusion of either motor phenotype or aetiological classification provided some additional information (χ^2-test for nested models p=0.026 and p=0.045, respectively). The direction of all effects remains the same in the models with two variables compared to the models with just one variable. A model with both GMFCS level and motor phenotype is not significantly improved by adding the aetiological classification (χ^2-test for nested models).

The BFMDRS motor score (132 patients) was significantly associated with age of FMD onset (p<0.001) with higher values corresponding to an earlier FMD onset (c.f. Table 3). When BFMDRS was included in the model, GMFCS level was the only

other explanatory variable attaining significance (χ^2-test for nested models P<0.001), despite the fact that both are strongly correlated (Spearman correlation of 0.76).

		Median age at overall FMD onset [95% CI]	Median age at hips onset [95% CI]	Median age at peripheries onset [95% CI]
All patients (no explanatory variables)		7.8 [6.6 to 9.0]	11.7 [9.5 to 14]	14.4 [11.5 to 17.3]
Aetiological Classification	Primary(-Plus)	>21 [15.5 to >21]	>21 [16.0 to >21]	>21 [16.0 to >21]
	Secondary	6 [5 to 7.1]	9.1 [7.4 to 10.9]	12.1 [9.8 to 14.4]
	Heredodegenerative	7.4 [4.4 to 10.4]	10.3 [5.2 to 15.3]	11.2 [6.3 to 16.1]
Motor Phenotype	Pure Dystonia	8.6 [7 to 10.3]	14.4 [10.8 to 18]	14.2 [10.9 to 17.5]
	Mixed Dystonia-Spasticity	4 [2.8 to 5.3]	5.1 [3.5 to 6.8]	10 [7.2 to 12.7]
	(Other)	20.9 [11 to >21]	>21 [12.2 to >21]	>21 [12.8 to >21]
GMFCS	Level I-II	>21 [18.8 to >21]	>21 [20.5 to >21]	>21 [20.1 to >21]
	Level III-IV	9.9 [7.3 to 12.5]	16.3 [10 to >21]	13.2 [8.9 to 17.4]
	Level V	5.1 [4.2 to 5.9]	7.1 [5.8 to 8.3]	10.2 [8.5 to 11.9]
BFMDRS	40	18.3 [12.7 to >21]	>21 [12.8 to >21]	>21 [14.5 to >21]
	80	9.8 [8.3 to 11.3]	14.5 [10.4 to 18.6]	13.6 [11.1 to 16.2]

Table 3. Median age at onset of fixed musculoskeletal deformities in different body regions as estimated by univariate accelerated failure time models. The 95% confidence intervals refer to the median and do not represent the expected ages for 95% of the population. Note the key limitation that this model assumes that FMD in any given body region will eventually occur. To avoid extrapolating, estimates greater than 21 years are not given. Results for other body regions are not shown, as the sample size was insufficient to give useful estimates.

Considering the different body regions, similar relationships were seen with earlier onset of FMD with increasing GMFCS level (Table 3). For hip FMD, an earlier onset of significant functional deformity was seen with a mixed dystonic-spastic motor phenotype compared to a pure dystonic phenotype and with secondary or heredodegenerative aetiological classification compared to primary or primary-plus classification (Table 3). After accounting for GMFCS level in the model, motor

phenotype was the only variable that provided additional information (χ^2-test for nested models p<0.001).

Discussion

Our current study explored factors relating to age of FMD onset in childhood dystonia by evaluating FMD status at the time of referral to our service. FMD onset was earlier for children with secondary/heredodegenerative conditions compared to primary dystonia (likely due to the more severe dystonia), and mixed dystonia-spasticity compared to pure dystonia.

FMD arising in CAYP with hypertonicity has been best studied in CP, which has an incidence in the developed world of 1 to 3 per 1000 live births[18]. Studies describing contractures in patients with CP have often not distinguished clearly between spastic and dystonic motor phenotypes, and when this distinction is made children with dystonic motor phenotypes represent only a small minority of the overall cohort. This issue is further complicated when one considers that these phenotypes are often coincident[19 20].

FMD involving the hips was seen most commonly in our cohort (74% of CAYP with FMD). Estimates of the prevalence of hip dislocation in CP vary from 1.5 to 75%, correlating with the severity of motor impairment[21]. Hip flexion contractures are amongst the most common musculoskeletal deformities seen in CP[22] and increasing impairment of function has been described with increasing severity of joint restriction[23]. In our cohort, after accounting for the effect of GMFCS level, an earlier

onset of FMD with hip deformity was seen in CAYP with a mixed dystonic-spastic phenotype compared to a pure dystonia, suggesting this group require closer hip surveillance. Similarly, scoliosis has been reported in 15-80% of patients with CP, risk appearing to increase with the extent of body involvement and severity of motor impairment[24]. In our cohort an earlier onset of spinal deformity was estimated with increasing GMFCS level though age of onset but not motor phenotype.

In our study, the effect of aetiological classification on estimated age at FMD onset became insignificant once either motor phenotype or motor severity were included in the model. CAYP with secondary and heredodegenerative groups had more severe motor disorders, with higher GMFCS level. This is may be a result of a referral bias, due the perceived efficacy of interventions such as DBS in the primary dystonia group. As the efficacy of interventions such as DBS and ITB for secondary dystonia is less well established, referral for evaluation may tend to be limited to more severely affected patients within these groups.

Whilst a great emphasis has been placed upon the role of physiotherapy and other such interventions, there is little evidence to support stretch alone in the prevention of contracture in children with hypertonia[25]. Other early interventions to treat spasticity (including ITB) have been suggested to reduce the need for subsequent orthopaedic surgery to correct contractures/deformities[10 26]. Whilst this may relate to a slowing of progression to FMD, it is also possible that this is due to decreased pain/discomfort associated with established FMD following intervention. The efficacy of such interventions as a preventative measures in dystonia is less clear.

BFMDRS motor scores were available for only 47% of the cohort. In our clinical practice BFMDRS assessments are limited to CAYP for whom an objective measure of dystonia is required prior to an intervention, e.g. new medication, DBS/ITB etc. The proportion of CAYP with FMD amongst the group for whom BFMDRS motor scores were available was significantly lower, potentially limiting applicability of findings in this subgroup to the cohort as a whole. Parametric accelerated failure time models indicated that both BFMDRS and GMFCS were highly informative for predicting the age of FMD onset. Future work is needed to determine whether interventions producing changes in BFMDRS scores without changing the GMFCS classification for CAYP slow the rate of progression to FMD.

A number of limitations to our study must be acknowledged. Data was collected from a convenience sample referred to our supra-regional service, likely to represent the more severe end of childhood dystonia. Data was collected retrospectively, with the attendant problems of such studies. A pragmatic definition of musculoskeletal deformity was used. Whilst we believe this definition is appropriate in focusing attention upon deformity adversely affecting the lives of CAYP, it limits direct comparisons with other studies. Motor phenotyping was categorical, and, consequently, reductive. CAYP with co-incident spasticity often exhibited elements of choreoathetosis. Additionally, CAYP, particularly those with CP, with minimal choreaothetosis, with a predominantly dystonic movement phenotype where categorised as “Dystonia”. Tools have recently been developed which enable the separate quantification of dystonia and choreoathetosis in CAYP[27]. This Dyskinesia Impairment Scale (DIS) requires a specifically protocolled video recording to apply, and cannot be applied retrospectively. BFMDRS scores were not available for a

significant proportion of our cohort. We have captured data at the point of assessment by our service. A variable period of time may have passed between the development of FMD and the point of assessment. Prospective studies would be required to better define the precise timing of the establishment of deformity, though, again, defining the point at which restricted range of movement constitutes fixed deformity is problematic. We have assumed that, without intervention, progression to FMD will eventually occur for all patients and only the rate of this progression varies for each individual. The BFMDRS score is known to have limitations when applied to secondary dystonias[28]. As noted in the methods session, the GMFCS has been validated in children with CP, but not in children with other causes of dystonia. In other conditions, motor function may not be stable over time (particularly in the heredodegenerative group), and could potentially decline rapidly in a short time. We would recommend the term "GMFCS equivalent" as a caveat in this patient population, to acknowledge this limitation.

The most important limitation, as discussed above, is the referral bias to our centre.

In conclusion, we explored the prevalence of FMD in a large cohort of CAYP with dystonic motor disorders referred to our service. A high prevalence of FMD was found, particularly around the hip. Earlier FMD onset was seen amongst CAYP with secondary and heredodegenerative dystonias, likely due to more severe motor impairment, and those with a mixed dystonic-spastic phenotype. These findings are comparable to findings in children with spastic CP and support the close monitoring of all CAYP with dystonia for contracture development. Given the potential of FMD to limit the benefits of interventions to manage childhood dystonia, we would

recommend that for children with dystonia (particularly the more severe cases as determined by either GMFCS or scales such as the BFMDRS), early referral for specialist assessment should be considered.

All authors confirm no conflicts of interest to report.

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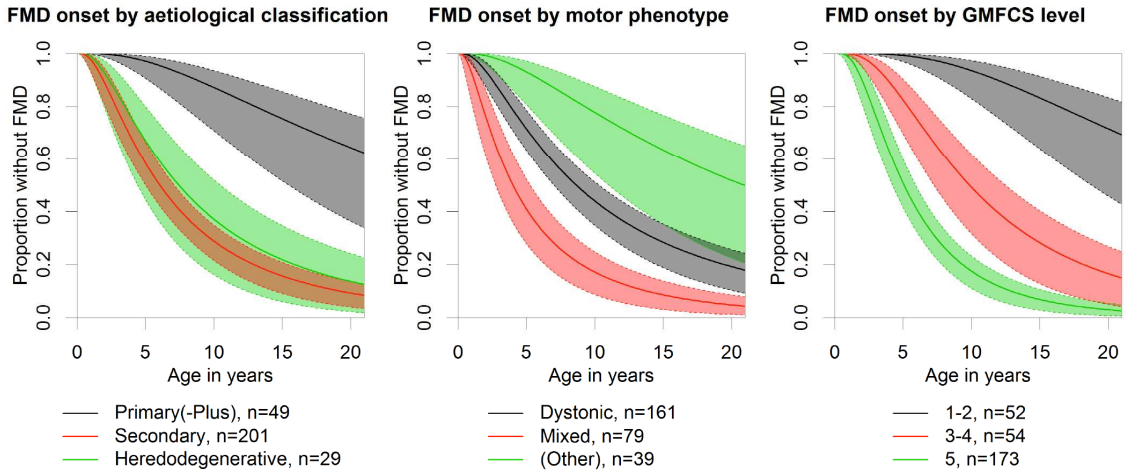
Figure Legends

Figure 1. Parametric accelerated failure time models for age of FMD onset with one explanatory variable each. Shown are the median curve for each subgroup (thick line) together with 95% confidence intervals (shaded area bordered by dashed lines). Left: aetiological classification, centre: motor phenotype, right: GMFCS levels.



Highlights:

1. Fixed Musculoskeletal Deformity (FMD) are common in children with dystonia at the time of referral
2. Progression to FMD is faster with worsening GMFCS level
3. Progression to FMD is faster in children with both dystonia and spasticity